## REMARKS

Claims 9, 11, 18, 21, 22 and 27 have been amended. Claims 10, 19-20 and 24-26 have been canceled without prejudice. Support for the amendments and can be found throughout the specification including the Drawings and claims as filed originally. No new matter has been added. Applicant appreciates the Examiner's acknowledgement of Applicant's claim for foreign priority based on an application filed in Denmark on January 23, 2001. A certified copy of the PA 2001 00118 application will be submitted herewith.

## Claim Objections

> The Examiner states, "Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 26 limits claim 25 to "said test cell comprises the chloride channel CIC-7", but claim 25 already has the limitation that the "test cell comprises the chloride channel CIC-7."

Claim 25 has been canceled, thereby obviating this basis for objection. Applicants respectfully requests reconsideration.

> Claim 18 is objected to because of the following informalities: In line 4, "of the compounds" should be removed. Appropriate correction is required."

Claim 18 has been amended to delete the phrase "of the compounds". Applicants respectfully requests reconsideration.

**Claim Rejections**

1) Claims 9, 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Aromataris et al (British Journal of Pharmacology (1999) volume 126, pages 1375-1382).

> The Examiner states, "Claims 9, 18 and 23 are drawn to a method of screening chemical compounds for activity in treatment, prevention of alleviation of an osteoclast related bone disease in a subject that comprises providing a test sell that comprises one or more chloride channels of the CIC family, subjecting the cell to the compound and measure the ability of the compound to block the chloride channels.
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> Aromataris et al teaches expression of the rat CIC-1 channel in Sf-9 cells, exposing the cells to RS-(+) 2-(4-chlorophenoxy) propionic acid and its enantiomer and measuring the activity of the chloride channel using patch-clamp experiments (abstract, page 1376, left column bridging right column and page 1377, Figure 1 and Table 1). Although Aromataris et al does not disclose that the method is to be used for evaluating the activity of the compound in the treatment, prevention or alleviation of an osteoclast related bone disease in a subject as recited in the preamble of the instant claims, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao,* 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Roble,* 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, there is no difference in the process steps recited in the claims and the process disclosed in Aromataris et al, and there does not appear to be any active process steps implied by the preamble which are not comprised by the method of Aromataris et al. Therefore, absent evidence to the contrary, the process of Aromataris et al is the same as the process claimed.
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> Claims 9, 18 and 23 were rejected as lacking novelty under 35USC102(b)

as being anticipated by Aromataris et al. Nothing in Aromataris et al concerns itself with the chloride channel C1C-7. Claims 9 and 18 (and therefore Claim 23) have been amended to require screening using a cell containing the C1C-7 chloride channel or to establish whether a test compound blocks the chloride channel C1C-7. All of the claims are therefore novel over the disclosure of Aromataris et al. Applicants respectfully requests reconsideration.

2) Claims 9, 18 and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by Pusch et al (Molecular Pharmacology (2000) volume 58(3), pages 498-507).

> The Examiner states, "Claims 9, 18 and 23 are drawn to a method of screening chemical compounds for activity in treatment, prevention of alleviation of an osteoclast related bone disease in a subject that comprises providing a test sell that comprises one or more chloride channels of the CIC family, subjecting the cell to the compound and measure the ability of the compound to block the chloride channels.
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> Pusch et al teaches expressing human CIC-1, rat CIC-2, human CIC-5 and the T. marmorata channel CIC-0 in X. laevis oocytes and determining the effects of enantiomers of 2-9p-chlorphenoxy)propionic acid (CPP) and its analogs on the cells by two-microelectrode voltage-clamp measurements and patch clamp measurements for analysis of the channel activity (abstract, page 498, right column, last paragraph to page 500, left column and page 502, right column, third full paragraph through page 503). Although Pusch et al does not disclose that the method is to be used for evaluating the activity of the compound in the treatment, prevention or alleviation of an osteoclast related bone disease in a subject as recited in the preamble of the instant claims, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *in re Hirao,* 535 F.2d 67, 190

> USPQ 15 (CCPA 1976) and *Kropa v. Robie,* 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, there is no difference in the process steps recited in the claims and the process disclosed in Pusch et al, and there does not appear to be any active process steps implied by the preamble which are not comprised by the method of Pusch et al. Therefore, absent evidence to the contrary, the process of Pusch et al is the same as the process claimed.

Claims 9, 18 and 23 were rejected under 35US102(a) as being anticipated by Pusch et at. Once again, the claims have been amended to be limited to the C1C-7 chloride channel. Pusch et al is not concerned in any way with determining whether the compounds block the chloride channel C1C-7. Thus, claims 9, 18 and 23 are novel. Applicants respectfully requests reconsideration.

3) Claim 9-11 and 18-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The Examiner states, "Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, relative skill in the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant discussed below.
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> *Nature of the invention:* The claims are drawn to method of screening chemical compounds for activity in treatment, prevention of alleviation of an osteoclast related bone disease in a subject that comprises providing a test sell that comprises one or more chloride channels of the CIC family, subjecting the cell to the compound and measure the ability of the compound to block the selected chloride channels.
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> *Breadth of the claim.* The claims are broad in that they encompass screening various chemical compounds for their ability

to treat any osteoclast disorder by determining the ability of the compound to modulate any CIC chloride channel in any test cell.

*Guidance in the specification/Existence of a working example:* The specification has not demonstrated that any of the CIC family members are involved in osteoclast disorders. The specification provides working examples that demonstrate the expression by northern blot analysis of CIC-7 in human osteoclasts and upregulation during osteoclast differentiation, but the expression of the other two tested CIC channels, CIC-3 and CIC-6, was not detected (page 14-15). The applicant's conclude that "CIC-3 and CIC-6 are not significantly expressed in osteoclasts" since they are only detected in the more sensitive RTPCR analysis (page 15).

Furthermore, the specification provides HEK293, which are human embryonic kidney cells, recombinantly expressing CIC-3, CIC-6 and CIC-7 for screening compounds that have the ability to block the chloride channels by patch clamp analysis. The specification has not provided methods on how to select for compounds that block CIC-7 and not CIC-1, CIC-2, CIC-4, CIC-5, CIC-Ka and CIC-Kb in any test cell. In addition, the specification has not demonstrated that identification of any compound that can block any CIC family member or specifically CIC-7 will result in a potential compound that can treat, prevent or alleviate an osteoclast disorder. In particular, a correlation between the level of inhibition of any chloride channel by a compound and the ability of that compound to be useful as a therapeutic has not been demonstrated.

*State of the art/Predictability of the art:* At the effective time of filing and presently, the only CIC family member known to be involved in an osteoclast disorder is CIC-7. Specifically, briefly prior to the effective filing date of the instant application, Kornack et al demonstrated a correlation between loss of the CIC-7 chloride channel and osteopetrosis (Kornack et al. Cell (2001) volume 104, pages 205-215 as cited in the IDS submitted on February 13, 2004), but no relation between CIC-7 and osteoperosis, Paget's disease of bone or osteolytic cancer invasion had been identified. The other family members have not been shown to be involved in osteoclast disorders. Rather, the other members have been shown to be involved in renal, muscular and neurological disorders. For instance, CIC-3 has been shown to be involved in CNS degeneration in a mouse model, CIC-1 is involved in human myotonia, CIC-5 is involved in kidney disorder such as Dent's disease and the role of CIC-6 in human disease remains unknown

(George et al. Current biology (2001) volume 11, pages R620-R628; see page R621, Table 1; Jentsch et al. Current Opinion in Neurobiology (2005) volume 15, pages 319-325; see page 321, Table 1).

*Quantity of experimentation:* A large amount of experimentation would be necessary to determine if the chemical compounds found to block CIC chloride channels in any test cell would provide potential compounds for the treatment of any osteoclast disorders since the specification nor the art has demonstrated that all the CIC family channel members are involved in all osteoclast disorders.

*Conclusion:* In order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to screen chemical compounds as potential therapeutic agents for osteoclast related disorders for their ability to block CIC chloride channels. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize a role for CIC chloride channels other than CIC-7 in the normal or diseased osteoclast. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Applicants respectfully disagree. The Examiner acknowledged that the specification provides working examples that demonstrate that the expression of C1C-7 is found in osteoclasts but not CIC-3 and CIC-6. First, the Examiner has acknowledged that the specification provides HEK293 cells modified to express C1C-3, CIC-6 and C1C-7 for screening compounds. As it is not exactly clear from the Examiner's acknowledgement of the relevant teaching, Applicants take this opportunity of stressing that Example 2 of the application describes the production of three different cell lines from HEK293 cells. These respectively express C1C-3, CJC-6 and C1C-7 individually. Thus, the C1C-7 cells can be used to screen for compounds which block C1C-7 and of course the C1C-3 and CIC-6 cells can be used respectively to check that the compounds in question do not also block CIC-3 or CIC-6.

The Examiner objects that the specification has not provided methods on

how to select for compounds that block CIC-7 but which do not block other named chloride channels.

The specification does of course contain on page 3 a specific teaching that one should select for this pattern of blocking activity. Applicants submit that this, taken together with the teaching of how to provide cells expressing specific chloride channels, is all that a person skilled in the art requires by way of instruction. It is common sense starting from this point that all that one needs to do is to conduct a first screen for compounds which are active in blocking chloride channel transport in the cells expressing C1C-7 and then to run similar screens of those compounds which pass the C1C-7 screen, but this time checking that they do not have a similar blocking action in cells where other C1C channels are expressed.

The teaching of how to express specific chloride channels which is exemplified by C1C-3, CIC-6 and C1C-7 is clearly readily extendable by the skilled person to the other named chloride channels.

The Examiner has further commented that the specification has not demonstrated that identification of any compound that can block any CIC family member, or specifically C1C-7 will result in a "potential compound" that can treat or alleviate an osteoclast disorder. In particular, the Examiner notes that a correlation between the level of inhibition of any chloride channel by a compound and the ability of that compound to be useful as a therapeutic has not been demonstrated.

However, in Applicants' submission the Examiner here goes beyond what Claims 9 and 18 should properly have been understood to be requiring. As these claims are directed to methods for screening, they should of course be understood as relating to the identification of compounds which have an increased likelihood of being suitable for use in such treatment. The invention is based upon the discovery by the inventors that C1C-7 is expressed in osteoclasts (Example 1).

Since osteoclasts have to secrete an acid environment in order to achieve resorption of bone, it is of course prima facie highly likely that compounds which interfere with their ability to transport chloride iron will modulate their bone resorbing ability. The specification does not assert that every compound which has the ability to block the chloride channel C1C-7 will be useful in treatment. The purpose of a screen is to identify compounds which are worth further investigation for use in such treatment.

Claim 9 as amended no longer refers to the treatment, prevention of alleviation of disease. It requires merely a method for screening for activity in blocking the chloride channel C1C-7 and sets out a method of doing this.

Claim 18 as amended makes clear that the screening is for compounds having potential activity for treatment purposes.

The Examiner has commented that C1C-7 is known now to be involved in an osteoclast disorder, reference being made to Kornack et al but that other family members have not been shown to involved in osteoclast disorders. The amended claims submitted herewith are specifically concerned with screening for the blocking of channel C1C-7 rather than other chloride channels. It is therefore apparent that the requirement for enablement for conducting a screen for potential therapeutic activity against osteoclast related disorders is satisfied and that based on Kornack et al and the teaching of the application it is likely that compounds satisfying the screen will have potential for use in the relevant treatment. It is said by the Examiner that a large amount of experimentation will be necessary to determine if the chemical compounds found to block CIC chloride channels in any test cell would provide potential compounds for the treatment of any osteoclast disorders as the specification and the art has not demonstrated that all of the CIC family channel members are involved in all osteoclast disorders. It appears to Applicants that this objection should be rendered moot by the limitation to requiring blocking of C1C-7. However, Applicants would comment

that in connection with compounds which block CIC-7, the burden of experimentation is not large. To determine whether a compound identified by the screen may be of therapeutic value would involve only the routine tasks of exposing osteoclasts to the relevant compound in a bone resorption assay of a known kind followed by suitable *in vivo* testing. The enclosed paper by Schaller et al which demonstrates that a compound identifiable using screening methods as described in the specification has *in vivo* effect in rats in modulating osteoclast activity resulting in the prevention of bone loss. This paper verifies the predictive teaching of the current application. Applicants respectfully requests reconsideration.

4) The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

> The Examiner states, "Claim 9 recites the limitation "the channel compound" in line 6. There is insufficient antecedent basis for this limitation in the claim.".

Claim 9 has been amended to include reference to "chemical compound" and has deleted reference to "channel compound". Applicants respectfully requests reconsideration.

> 5) The Examiner states, "Applicant is advised that should claims 9-11 be found allowable, claims 18, 23, 24 and 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants respectfully disagree. The distinguishing limitation between independent claims 9 and 18 is that in claim 9 the screening method is directed to compounds with actual activity in blocking the C1C-7 chloride channel, whereas in claim 18the screening method is directed to compounds which have potential activity for blocking the C1C-7 chloride channel and may be useful in the treatment, prevention, or alleviation of an osteoclast related bone disease in a subject. Thus, the subject matter of the two claims are different. The other claims mentioned by the Examiner are all dependent from either claims 9 or 18. Applicants respectfully requests reconsideration.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this Amendment. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record. Should it be required, the Applicants conditionally petition for a extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below, charge Deposit Account No. **04-1105** for any required fee.

Respectfully submitted,

Date: June 22, 2006

Gregory B. Butler, PhD, Esq
Registration No. 34,558
EDWARDS ANGELL PALMER
& DODGE LLP
P. O. Box 9169
Boston, MA 02209
Tel. (617) 439-4444
Fax Nos. (617) 439-4170 / 7748
Customer No.: 21874

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